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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/500,047	02/08/2005	Jon H. Rasmussen	C2432.0057	9121

32172 7590 04/09/2007

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EXAMINER	
KOSAR, ANDREW D	
ART UNIT	**PAPER NUMBER**
1654	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/09/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/500,047	RASMUSSEN ET AL.	
	Examiner	Art Unit	
	Andrew D. Kosar	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 14-26 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 14-26 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date 6/25/04.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 14-26 are pending.

Priority

Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Abstract

The abstract of the disclosure is objected to because the abstract asserts that the tripeptides are 'novel', which is in direct contrast to the applied art (below) and the abstract should not refer to purported merits of the invention.

Correction is required. See MPEP § 608.01(b).

Claim Objections

Claim 20 is objected to for having more than one period in the claim. MPEP § 804.01(m) states that, "Each claim begins with a capital letter and ends with a period. Periods may not be used elsewhere in the claims except for abbreviations. See *Fressola v. Manbeck*, 36 USPQ2d 1211 (D.D.C. 1995)."

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 15-24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 15-24 recite, for example, Lys(iPr,P^4) and it is unclear whether the side chains are protected one or both members within the parenthetical expression. To clarify the ambiguity, the claims would more appropriately recite Lys(X) with X defined separately in the claim as being, in this example, selected from iPr or P^4.

Claims15 and 20 recite, "such as Boc" and claims 23 and 24 recite "in particular an acetyl group" which renders the claims vague and indefinite, as it is unclear whether the Boc or acetyl is a limitation in the claim or merely exemplary of protecting groups that can be employed in the method.

Furthermore, a broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949).

Claim 19 lacks clear antecedent basis, as claim 17 does not provide antecedent basis for 'the heptapeptide of the formula (VI)".

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 25 is rejected under 35 U.S.C. 102(b) as being anticipated by FUNK (US Patent 5,710,246).

The claim is drawn to the peptide Ac-D-2Nal-D-4ClPhe-D-3Pal-OH.

Funk teaches the peptide Ac-D-2Nal-D-4ClPhe-D-3Pal-OH (e.g. Example 45, column 40, line 39).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 25 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Funk, *supra*, in view of O'NEILL (US Patent 6,235,734 B1).

The instant claims are presented *supra* and are additionally drawn to the peptide Boc-D-2Nal-D-4ClPhe-D-3Pal-OH.

The teachings of Funk are presented *supra*. Funk additionally teaches the peptides Boc-D-2Nal-D-4ClPhe-D-3Pal-OMe, Boc-D-2Nal-D-4ClPhe-D-3Pal-OAll and Boc-D-2Nal-D-4ClPhe-D-3Pal-OBzl (e.g. claim 20; column 13, lines 5-7; synthesis in Example 25, column 24).

Further, Funk teaches the synthesis D-2Nal-D-4ClPhe-D-3Pal-OH

O'Neill teaches that nitrogen protecting groups are known in the art and, "include[e] t-BOC, CBZ, methyl, benzyl, trifluoroacetyl, acetyl and benzoyl. (column 13, line 65 to column 14, line 61).

The difference between that which is claimed and the teachings of Funk, is that while Funk teaches the peptide with an N-acetyl group, or the Boc protected peptide which has been esterified, Funk does not teach the Boc protected peptide which has not been esterified.

The MPEP states, "A *prima facie* case of obviousness may be made when chemical compounds have very close structural similarities and similar utilities. "An obviousness rejection based on similarity in chemical structure and function entails the motivation of one skilled in the art to make a claimed compound, in the expectation that compounds similar in structure will have similar properties." *In re Payne*, 606 F.2d 303, 313, 203 USPQ 245, 254 (CCPA 1979). See *In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963) and *In re Dillon*, 919 F.2d 688, 16 USPQ2d 1897 (Fed. Cir. 1991)." *See* MPEP § 2144.09.

Here, the compounds of Funk differ from the instant claims either at the N-terminus (acetyl vs Boc protecting group) or at the C-terminus (H vs methyl). The compounds are both used in further synthesis of LHRH analogs, and acetyl and Boc are both well known N-protecting groups. Thus, it would have been obvious at the time of the invention to have made Boc protected peptide, Boc-D-2Nal-D-4ClPhe-D-3Pal-OH, with the expectation that the

compound would function as the N-acetyl counterpart in the synthesis of LHRH analogs. One would have been motivated to have made the Boc protected peptide in order to make a compound that would function similarly in the synthesis of LHRH analogs. One would have had a reasonable expectation for success in making the Boc-protected peptide, since the N-acetyl peptide is known, and the esterified Boc-protected peptide is known and incorporation of a protecting group is widely practiced in the peptide arts.

Furthermore, Funk and O'Neill are relied upon for the reasons discussed above. If not expressly taught by the references, based upon the overall beneficial teaching provided with respect to the LHRH analog precursors and N-protecting groups, the adjustments of particular conventional working conditions (e.g., selecting one or more suitable protecting groups), is deemed merely a matter of judicious selection and routine optimization which is well within the purview of the skilled artisan.

From the teachings of the reference, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Claims 14-16, 18, 20-22, 25 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Funk, *supra*, in view of O'Neill, as applied to claims 25 and 26 *supra*, and in further view of HUBBS (US Patent 5,322,931) and VEBER (US Patent 4,098,777).

The instant claims are further drawn to the method of making X-D-2Nal-D-4ClPhe-D-3Pal-OH where X is Ac or Boc, and to the method of making LHRH antagonists using said compounds. The teachings of Funk and O'Neill are presented *supra*.

Funk further teaches the synthesis of synthesis of the protected compound P^1-D-2Nal-D-4ClPhe-D-3Pal-O-P^4 (Scheme III, column 11) from reaction of P^1-D-2Nal-OH with P^1-D-4ClPhe-D-3Pal-O-P^4. P^1-D-4ClPhe-D-3Pal-O-P^4 is synthesized from P^1-D-4ClPhe-OH and the HCl salt of D-3Pal-O-P^4.

Funk teaches the formation of Ac-D-2Nal-D-4ClPhe-D-3Pal-Ser(Bzl)-NMeTyr(Cl_2Bzl)-D-Lys(Nic)-Leu-Lys(iPr)-Pro-D-Ala-NH_2 from the reaction of Ac-D-2Nal-D-4ClPhe-D-3Pal-OH with Boc-Ser(Bzl)-NMeTyr(Cl_2Bzl)-D-Lys(Nic)-Leu-Lys(iPr)-Pro-D-Ala-NH_2. (Example 40, column 40).

Hubbs teaches, "The condensation reaction of the two fragments can be accomplished by standard techniques, such as treatment of the two peptide fragments with condensation reagents such as a dehydrating agent (e.g. dicyclohexylcarbodiimide (DCC)) and an activating agent (e.g. N-hydroxysuccinimide (HONSu)) in an organic solvent. In one preferred embodiment, the activating agent is also a racemization inhibitor (e.g. HONSu)." (column 10, lines 5-13).

Veber teaches that OH protecting groups for serine are benzoyl, t-butyl and benzyl (column 6, lines 36-39) and protecting groups for other amino acids, e.g. Lys (column 9)

The difference between that which is claimed and the teachings of Funk, is that while Funk teaches the basic methods claimed, Funk does not specifically teach the use of HONSu in the coupling step or the specific use of tBu protection of side chains.

It would have been obvious to one of skill in the art to have used HONSu in the synthesis methods in order to inhibit racemization of the product. One would have been motivated to have used HONSu because in addition to being an activating agent in the coupling step, HONSu is a racemization inhibitor. One would have had a reasonable expectation for success in using HONSu in the method of making the LHRH precursors and antagonists, as the method is generally taught by Funk and the use of HONSu in peptide synthesis is known in the art as an activator for coupling that is also an inhibitor of racemization.

With regards to the different protecting groups, if not expressly taught by the references above, based upon the overall beneficial teaching provided with respect to the LHRH analog precursors and N-protecting groups and/or side chain protecting groups, the adjustments of particular conventional working conditions (e.g., selecting one or more suitable protecting groups), is deemed merely a matter of judicious selection and routine optimization which is well within the purview of the skilled artisan.

From the teachings of the reference, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Claims 14-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Funk, *supra*, in view of O'Neill, Hubbs and Veber, as applied to claims 14-16, 18, 20-22, 25 and 26 *supra*, and in further view of GEFTER (US Patent 6,699,833 B1).

The claims are additionally drawn to synthesis of the LHRH analog where AA2 is D-Asn. The teachings of Funk, O'Neill, Hubbs and Veber are presented *supra*.

Gefter teaches the LHRH analog where AA2 is D-Asn (e.g. claim 26).

The difference between that which is instantly claimed, and the teachings of Gefter, is that while Gefter teaches the product formed, Gefter does not teach the synthesis as instantly claimed.

It would have been obvious to have synthesized the product using any synthetic methodology, including synthesis by the method of Funk as presented *supra*. One would have been motivated to have synthesized the peptide via any means, including modifying the method of Funk to use protecting groups and HONSu, in order to synthesize the compound and to inhibit racemization of the product. One would have had a reasonable expectation for success in practicing the method to make the product with AA2 being D-Asn, as peptide synthesis is well known and widely used in the art.

With regards to the different protecting groups, if not expressly taught by the references above, based upon the overall beneficial teaching provided with respect to the LHRH analog precursors and N-protecting groups and/or side chain protecting groups, the adjustments of particular conventional working conditions (e.g., selecting one or more suitable protecting groups), is deemed merely a matter of judicious selection and routine optimization which is well within the purview of the skilled artisan.

From the teachings of the reference, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at

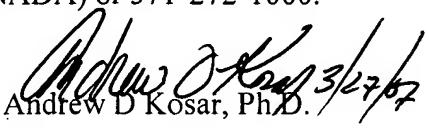
the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Andrew D. Kosar whose telephone number is (571)272-0913. The examiner can normally be reached on Monday - Friday 08:00 - 16:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia J. Tsang can be reached on (571)272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.



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Art Unit 1654